



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES  
AND TOXIC SUBSTANCES

**MEMORANDUM**

**DATE:** January 7<sup>th</sup>, 2015

**SUBJECT:** **Bifenthrin:** Summary of Hazard and Science Policy Committee (HASPOC)  
Meetings of July 31, 2014: Re-evaluation on the need for an acute inhalation  
toxicity.

**PC Code:** 128825  
**Decision No.:** N/A  
**Petition No.:** N/A  
**Risk Assessment Type:** N/A  
**TXR No.:** 0057021  
**MRID No.:** N/A

**DP Barcode:** N/A  
**Registration No.:** N/A  
**Regulatory Action:** N/A  
**Case No.:** N/A  
**CAS No.:** N/A  
**40 CFR:** N/A

**FROM:** Jonathan Leshin  
Executive Secretary  
Hazard and Science Policy Committee  
Antimicrobials Division (7510P)

**THROUGH:** Jeff Dawson, Co-Chair  
Anna Lowit, Ph.D, Co-Chair  
Hazard and Science Policy Committee  
Health Effects Division (7509P)

**TO:** William Irwin, Ph.D., DABT, Toxicologist  
Michael Metzger, Branch Chief  
Registration Action Branch 5  
Health Effects Division (7509P)

**MEETING ATTENDEES:**

**HASPOC Members:** Anna Lowit, Elissa Reaves, Elizabeth Mendez, Jeff Evans, Jeff Dawson,  
John Kough, Jonathan Chen, Michael Metzger, P.V. Shah, Ray Kent, Jonathan Leshin, Chris  
Schlosser, Uma Habiba

**Presenter:** William Irwin

**Other Attendees:** Rebecca Dzubow, Kathy Schneider, Billy Smith, Wade Britton

## **I. PURPOSE OF MEETING**

The HED Hazard and Science Policy Council (HASPOC) initially met on April 26, 2012 to discuss whether a sub-chronic inhalation toxicity study is required to address the concern for repeated inhalation exposures resulting from the proposed and registered uses of bifenthrin. The HASPOC requested an acute inhalation study with neurobehavioral observations in lieu of the typical subchronic- inhalation study. The April 26, 2012 HASPOC memo contains the background details and rationale for the decision (TXR # 0056209). In response, FMC submitted a pharmacokinetic (PK) study to the agency comparing tissue dosimetry for the oral and inhalation routes for bifenthrin. FMC requested that the PK study be considered as support for waiving the acute inhalation toxicity study. The HASPOC met on July 31st to evaluate the bifenthrin PK study (MRID 49153401). Additionally, new inhalation MOEs were calculated and presented for bifenthrin uses.

## **II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENT:**

Bifenthrin is a pyrethroid insecticide/miticide used to control termites and insects in both agricultural and residential settings. Bifenthrin is currently registered as emulsifiable concentrate (EC), wettable-powder (WP), granular (G), and flowable-concentrate (FIC) formulations. Bifenthrin is registered for use by occupational handlers on a variety of agricultural commodities, and by occupational and residential handlers on turf and indoor environments (crack and crevice). Exposure to bifenthrin is expected to be short- and intermediate-term durations for occupational handlers and short-term for residential handlers and following use in residential settings. Bifenthrin may be applied with handheld, ground, and aerial equipment.

Neurotoxicity is the most consistently observed finding throughout the bifenthrin toxicity database, and neurotoxic effects provide the most sensitive endpoints for deriving PODs for risk assessment. Bifenthrin toxicology database provides no evidence of enhanced toxicity with increase in exposure (treatment) time since comparable No Observed Effect Levels (NOAELs) were obtained following acute, subchronic and chronic exposures. Comparable PODs were established in the acute (BMDL=3.1 mg/kg), subchronic (NOAEL=2.9 mg/kg/day) and the carcinogenicity (NOAEL = 3.0 mg/kg/day) studies. The inhalation POD (based on an oral study) is a BMDL<sub>1SD</sub> of 3.1 mg/kg based on reductions in motor activity seen at a BMD<sub>1SD</sub> of 4.1 mg/kg (Wolansky *et al* 2006).

## **III. INHALATION STUDY WAIVER REQUEST**

### ***A. Requirement for the inhalation study***

Previously, the Office of Pesticide Programs (OPP) used a set of criteria to determine whether or not an inhalation study could be waived. These criteria considered the scientific information available for the chemical, including its: (1) degree of irritation and corrosivity; 2) volatility; 3)

aerosol particle size; and 4) Acute Toxicity Category and extrapolated MOEs (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PODs were protective of potential inhalation toxicity varied. In many cases the oral POD was protective, but in some cases the inhalation PODs were significantly more sensitive. Based upon a retrospective analysis of pyrethroid toxicology studies, the inhalation study NOAEL for pyrethroids is on average 19 times lower than the oral study NOAEL (TXR 0056209). Currently, OPP uses a weight of the evidence (WOE) approach that builds upon OPP's experience using the criteria listed above and conclusions from the 2009 SAP. As approaches for route-to-route extrapolation continue to evolve and improve, OPP may incorporate additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of inhalation exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. OPP's interim WOE approach considers:

1. **Physical-chemical properties:** Vapor pressure and Henry's law constant are key considerations with respect to the volatilization after sprays have settled. Bifenthrin has a low vapor pressure ( $2.41 \times 10^{-5}$  Pa at 25 °C). However, low vapor pressure and/or Henry's law constant ( $7.2 \times 10^{-3}$  atm·m<sup>3</sup>/mol) does not preclude exposure to aerosolized droplets or particles/dusts.
2. **Use pattern & exposure scenarios:** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. It is, however, acknowledged that air blast and aerial applications are more likely to lead to higher occupational handler inhalation exposure, particularly to droplets, and may contribute to spray drift.
3. **Margins of Exposure (MOEs):** The MOE estimates for inhalation scenarios were calculated using an oral toxicity study and should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern as a benchmark for granting waiver requests. The 2009 analysis suggests this approach is appropriate for most pesticides, but not all. Using this interim WOE approach, MOEs at least 10 times greater than the level of concern will be considered in combination with other factors discussed here. For short-term inhalation exposure risk assessment, an oral POD of 3.1 mg/kg is used for calculating the MOEs.

The inhalation MOEs range from 600 to 1,800,000. Only two use scenarios of dozens have MOEs less than 1000 (i.e. mixing/loading of granules for aerial applications and mixing/loading/applying a liquid formulated termiticide). For residential handlers, spraying ornamentals resulted in the highest inhalation exposure (MOE = 8,400).

4. **Toxicity:** Bifenthrin is a neurotoxic insecticide that belongs to the pyrethroid class of chemicals. Pyrethroids induce neurotoxicity by interacting with sodium channels located in nerve cells, causing hyperpolarization and eventually blocking nerve conductance.

Tremors are the most consistent effect across all toxicity studies. The most robust study (Wolansky et al 2006) monitored decreased locomotor activity, and is the basis of the PODs used for risk assessment. Based on bifenthrin's toxicity profile, the severity of effects from oral exposure do not appear to increase substantially over longer durations. Bifenthrin has a moderate order of acute toxicity via the oral route (Category II) and a low order of acute toxicity via the dermal route (Category III) of exposure. The acute lethal inhalation study classifies bifenthrin as Category III, with a combined LC<sub>50</sub> value of 1.01 mg/L (male result is 1.1 mg/L and female result is 0.8 mg/L). Acceptable studies on the end-use products are also available. Formulated bifenthrin is neither an eye nor skin irritant, nor is it a dermal sensitizer.

## 5. Pharmacokinetic Study: Summary & Review

The doses selected for the study were based on the results of Wolansky et al (2006) study being used for the POD for bifenthrin of 3.1 mg/kg based on reductions in motor activity seen at a BMD<sub>1SD</sub> of 4.1 mg/kg. The PK study consisted of two groups of 15 male Sprague-Dawley rats, one each for the oral and inhalation routes. For the oral exposure, the nominal dose of 3.1 mg/kg bifenthrin technical was administered via gavage in 1 mL/kg corn oil. The measured dose was only 75% of the nominal dose. Rats were sacrificed following oral exposure at 2, 4, 6, 8, and 12 hours post-dosing (n=3 per time-point). Blood and brain tissue were collected and stored at approximately -80°C. Analysis of tissue samples were conducted at Frontage Laboratories using LC/MS/MS.

Nose-only inhalation exposure was administered for either 2 or 4 hours. The target dose for inhalation exposure was 3.1 mg/kg over the 4 hour exposure period. The two hour inhalation group (n=3) was immediately sacrificed at the end of the two hour exposure. A separate group (n=3) received a 4 hour exposure followed by immediate sacrifice. The remaining rats were exposed for four hours followed by 2, 4, or 6 hour recovery periods (n=3 for each time-point). The mean mass median aerodynamic diameter was estimated to be 1.79 µm based on the particle size distribution. The gravimetric and nominal chamber concentrations were 0.018 mg/L and 0.065 mg/L, respectively. The actual delivered inhalation dose was estimated to be 3.2 mg/kg at 4 hours of exposure.

The study did not include neurobehavioral measures. Instead, limited clinical observations were made. There were no mortalities during this study. The 2 and 4-hour time-point groups appeared active and healthy during their respective observation periods. Following exposure at chamber removal, all animals in the 6, 8, and 12-hour time-point groups (i.e., 2, 4, and 6 post-exposure) exhibited irregular respiration, which resolved by the time of each respective necropsy.

**Table 1. Summary of bifenthrin concentration in rat plasma samples (Extracted from p 25, MRID 49153401)**

Route of Exposure	Time Point (hr)	Mean (ng/mL)	SD
Inhalation	2	232.487	138.089
	4	158.035	23.037

Oral	6	106.640	41.803
	8	109.333	31.978
	12	34.994	1.725
	2	360.915	145.581
	4	316.982	141.654
Inhalation	6	105.811	44.937
	8	83.146	4.393
	12	25.168	7.978
	2	360.915	145.581
	4	316.982	141.654

The plasma concentration data (Table 1) are highly variable, particularly at the 2 hour time-points, for both oral and inhalation routes, due in part to the small sample size (3/time-point). Both routes show similar TK patterns: the concentrations are highest at the 2 and 4 hour time-points [during exposure for inhalation or soon after for oral] the dosing with decreases in plasma levels with time. The mean levels across the two routes are notably similar at the 6, 8, and 12 hour time-points.

**Table 2. Summary of bifenthrin concentration in rat brain samples (Extracted from p 26, MRID 49153401)**

Route of Exposure	Time Point (hr)	Mean (ng/mL)	SD
Inhalation	2	19.955	4.661
	4	64.045	24.766
	6	60.497	6.288
	8	61.530	7.610
	12	72.503	25.922
Oral	2	25.618	5.241
	4	74.255	13.524
	6	78.063	35.983
	8	83.145	20.641
	12	78.728	15.068

The brain concentration data (Table 2) are less variable compared to the plasma data in Table 1 and are notably similar at all time-points. Both routes show similar TK patterns: the concentrations are lowest at the 2 and show a rapid increase in concentration from 2 to 4 hours with similar levels from the 4 to 12 hour time-points.

In general, the agency supports the use of PK studies for route to route evaluation, considering dose selection, and human relevance. However, the agency notes some concerns with the PK study. The agency would have preferred that FMC submit a protocol for the PK and have dialogue on the study design prior to its conduct. The small

sample size (n=3/time-point) contributes to the variability in the plasma concentration data. Additional, later time-points to characterize the decrease in brain concentrations over time would also have been preferred. All these issues being noted, the agency believes that the information contained in the PK studies is sufficient to negate the need for further inhalation toxicity testing because it is clear that oral data will not underpredict the inhalation route for bifenthrin.

## **V. HASPOC RECOMMENDATION**

Based on a WOE approach considering of all the available hazard and exposure information for bifenthrin, the HASPOC concluded that an acute inhalation study with neurobehavioral metrics (Guideline 870.6200a) **is not required**. This decision was based on the following factors: (1) most MOEs are over 1000 for inhalation exposure in occupational and residential settings and only two use scenarios had inhalation MOEs less than 1000, (2) the physical chemical properties and the volatility of the compound, and (3) the PK study supports a conclusion that use of the oral study does not underestimate inhalation risk from bifenthrin.

## **REFERENCES**

PHARMACOKINETIC STUDY OF BIFENTHRIN TECHNICAL IN RATS BY ROUTE OF INHALATION AND ORAL EXPOSURE (Boulet et al, 2013, MRID 49153401)

Selim, S., "Kinetics of FMC 54800 in the Blood of Rats", FMC Corporation, Unpublished Study, MRID 00163069.

Scollon, E. J., J. M. Starr, S. J. Godin, M. J. DeVito and M. F. Hughes (2009). "In Vitro Metabolism of Pyrethroid Pesticides by Rat and Human Hepatic Microsomes and Cytochrome P450 Isoforms." *Drug Metabolism and Disposition* 37(1): 221-228.

Scollon, E.J., Starr, J.M., Crofton, K.M., Wolansky, M.J., DeVito, M.J., Hughes, M.F. (2011) "Correlation of tissue concentrations of the pyrethroid bifenthrin with neurotoxicity in the rat". *Toxicology* 290 (2011) 1– 6.